

REMARKS

Claims 1-20 and 23 are in the present application.

The Examiner has indicated that claims 7 and 10-16 would be allowable if placed in independent form. This amendment places those claims in independent form and, therefore, those claims should now be in form for allowance. Claim 1 of the present application has been amended in its preamble to delete surplus language and, in the definition of its stabilizing component, to clarify that that stabilizing components consists of the derivatized carbohydrate material. Housekeeping amendments have been made in several claims to insert appropriate punctuation and to utilize appropriate patent language.

Claim 20 has been amended to define a method of formulating the stable liquid formulation of a therapeutically active protein, rather than as the protein composition itself. Finally, claim 23 has been added to the present application (antecedent basis at page 1, lines 13-16, as well as original claim 1). This claim defines a device for delivering a therapeutic protein aerosol to the lower respiratory tract of a patient, the device comprising an electrostatic or electrohydrodynamic spray apparatus together with the stable liquid therapeutic protein formulation of the present invention.

In the office action, the Examiner rejected claim 1-6, 8, 9, 17-19 and 22, under 35 U.S.C. § 103(a), based on U.S. Patent 5,653,987 (Modi et al.). The Examiner contended that:

- Modi et al. teaches a liquid formulation for nasal delivery to a patient, comprising water (carrier), a protein (insulin, cytokine), sodium lauryl- β -D-maltopyranoside (derivatized carbohydrate), and other compounds such as oleic acid (excipient) and antioxidant; and

- it would have been obvious to one skilled in the art to determine the optimum amounts of carrier, organic solvent and excipient to develop a composition that would be effective in treatment as in the present invention.

For the reasons given below, the claims of the present application, as amended herein, are patentable over the disclosure in the Modi et al patent.

The liquid formula described in Modi et al. is an aqueous liquid formulation that is meant to be delivered orally (ingested) to the gastrointestinal tract, not aerosolized and delivered to the lungs via inhalation of an aerosol. Although the aqueous liquid formulations of Modi et al. are specifically developed for oral dosing, it is taught that they may be administered via the nose. However, Modi et al. recognizes that nasal delivery could cause sneezing or dripping as a result of irritation to the sensitive lining of the nose (see column 1, lines 46-52).

Although Modi et al. teaches that the disclosed formulations may be delivered nasally, as well as orally, it is clear from the context of the reference that Modi et al. contemplates conventional nasal delivery such as nasal spray or nose drops. Further, Modi et al. acknowledges that nasal delivery has problems, such as irritation of the mucus membranes of the nasal passages by the absorption enhancers and dripping of the drug from the nose. Where it is important that the amount of the administered dose of the drug be the same as the dose that is actually delivered, as in the case of insulin, nasal delivery is not a very precise method of delivering the drug. There is no suggestion in Modi et al. to deliver the drug to the lower respiratory tract, such as delivery via aerosol to the lung.

The aqueous formulations of Modi et al. are required to contain at least two absorption enhancing compounds selected from specific combinations (see column 2, lines 12-63). The

purpose of the absorption enhancer combinations is to enhance the solubility of the active agent in the stomach and the absorption of the drug across the intestinal wall (see column 1, lines 53-61). Example II and Table III of Modi et al. illustrate the importance of using the absorption enhancing combinations described in the patent. In Example II, a composition containing only one absorption enhancer was tested. The data in Table III show that an orally administered insulin formulation containing only sodium cholate as the absorption enhancer had little metabolic effect on blood glucose levels. One skilled in the art would be taught by Modi et al. that the presence of at least two absorption enhancers is essential and that the preferred combination includes a salt or ester of a bile salt (deoxycholate or chenodeoxycholate) together with a surface active agent, such as sodium lauryl sulfate or polyoxyethylene 9-lauryl ether (see column 3, lines 12-19). The Examiner is correct that the Modi et al. patent, at column 2, lines 24-25, describes N-lauryl- β -D-maltopyranoside as being a possible absorption enhancer. It should be noted that this material is one out of many absorption enhancers disclosed and, in fact, is not one of the preferred absorption enhancers. In any event, N-lauryl- β -D-maltopyranoside is only taught for use as part of an absorption enhancer combination.

The claims of the present application, as amended herein, are allowable over the Modi et al. patent for the following reasons:

(1) Claim 1 has been amended herein to insert “consisting of” language into the definition of the stabilizing component used in the present invention. Thus, in the present invention, the derivatized carbohydrate material described is included, but no other stabilizing component would be included in the compositions. Thus, claim 1 and those claims dependent from it clearly distinguish over the disclosure of Modi et al. which requires at least two

stabilizing components in order to have an operable composition. Thus, claims 1-6, 8, 9 and 17-19 clearly distinguish over the disclosure of Modi et al. There is absolutely nothing in Modi et al. that would suggest that a composition containing a single stabilizing component would be operable and, in fact, Example II and Table III suggest that such a composition would not be operable.

(2) Claim 20 distinguishes over the Modi et al. disclosure because claim 20 is drawn to a method of formulating a stable liquid protein formulation. The ability to formulate a liquid protein composition which exhibits long-term shelf stability is both new and unexpected. Typically, protein formulations are reconstituted just prior to use precisely because they are not stable. The present invention provides an important and unique way to stabilize such liquid protein formulations. The compositions in Modi et al. are taught to be absorbable when administered orally or through the mucus membranes of the nose. There is absolutely no suggestion in Modi et al. that those compositions would be stable over time. Thus, one skilled in the art would not look to the disclosure of Modi et al. when developing a method of formulating a stable liquid protein formulation as is defined in claim 20.

(3) Claim 23 defines the combination of an apparatus for delivering a protein containing aerosol to the lower respiratory tract of a patient. That apparatus comprises an electrostatic or an electrohydrodynamic aerosolization device which contains the stable liquid protein formulations of the present invention. There is absolutely nothing in Modi et al. which suggests that the disclosed compositions could be delivered to the lower respiratory tract of a patient. Further, there is absolutely nothing in Modi et al. that would suggest the use of the compositions in an electrostatic or an electrohydrodynamic aerosol device.

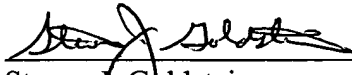
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(4) Finally, claims 7 and 10-16 have already been indicated as being allowable by the Examiner.

For the reasons set forth above, the claims currently pending in the present application are patentable over the Modi et al. patent. Accordingly, reconsideration of the rejection and allowance of the claims currently pending the present application are respectfully requested.

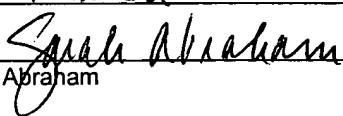
Respectfully submitted,

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<p align="center"><u>CERTIFICATE OF MAILING</u></p> <p>I hereby certify that a copy of this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on</p> <p><u>March 11</u>, 2005</p> <p> Sarah Abraham</p>
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